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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 03/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/487,318	REID ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2003 and 14 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8,9,12,14-19,38 and 45-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 8-9, 12, 14-19, 38 and 45-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 18, 2003 has been entered.

Amended claims 1-6, 8-9, 12, 14-19, 38 and 45-48 are pending in the present application, and they are examined on the merits herein.

Response to Applicants' Amendment

The rejection under 35 USC 112, First paragraph is withdrawn in light of Applicants' amendment.

The art rejections of record are withdrawn in light of Applicants' amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6 and 38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This is a new ground of rejection.**

Claim 6 recites the limitation "the alpha-fetoprotein" in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim. There is no recitation of any alpha-fetoprotein in claim 1 from which claim 6 is dependent.

Claim 38 is dependent on the cancelled claim 21. Therefore, it is unclear what Applicants intend to claim. The metes and bounds of the claim are not clearly determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6, 8, 12, 14-19 and 45-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Muench et al. (Blood 83:3170-3181, 1994; Cited previously). **This is a new ground of rejection.**

Muench et al. teach a method for isolating human fetal liver progenitors (page 3171, left-hand column, second to fourth full paragraph), said method comprises the steps of: (a) subjecting a suspension of human fetal liver cells to a density centrifugation at 1,000 g for 25 minutes (the debulking step); (b) collecting light density fetal liver (LDFL) cells; (c) deleting erythroid cells in the LDFL cell population using anti-GPA MoAb and sheep antimouse IgG-coated Dynabeads (a negative immunoselection step); (d) GPA^- LDFL cells were further enriched for $CD34^+$ cells (a marker associated

with mesenchymal stem cells) by panning using anti-CD34 antibody-coated tissue culture flasks (a positive immunoselection step).

As the method taught by Muench et al. contains the same steps (a) and (b) recited by the instant claims using the same starting material of human fetal liver, the LDFL cell population of any one of steps (b), step (c) and step (d) in the method of Muench et al. would inherently contain an enriched population of human liver progenitors having the recited characteristics.

Thus, the reference anticipates the instant claims.

Claims 1-6, 8-9 and 45-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Craig et al. (J. Exp. Medicine 177:1331-1342, 1993; Cited previously). **This is a new ground of rejection.**

Craig et al. disclose a method for the isolation of human hematopoietic progenitor cells derived from human fetal liver with a phenotype of Thy-1^+, $CD34^+$, $CD38^{low}$, $CD45RA^-$, $CD45RO^+$, $CD71^{low}$, and $CD117^{low}$ (See abstract, and left-hand column, second paragraph, page 1332). The method comprises the steps: (a) obtaining human fetal liver cells from elective, therapeutic abortions, in the 12-20^{th} week of gestation; (b) subjecting the human fetal liver cells to a density centrifugation using Ficoll-Paque to obtain low density mononuclear cells (left-hand column, page 1332, lines 24-26); (c) removing the interphase cells or the low density mononuclear cells; and (d) subpopulations of low density mononuclear cells were subsequently sorted by multiparameter flow cytometry, a form of positive immunoselection (right-hand column,

page 1335, second paragraph). Craig et al. further teach that in some samples, red blood cells were lysed by the addition of 10-fold excess of ammonium chloride lysing solution (left-hand column, page 1332, lines 30-32).

As the method taught by Craig et al. contains the same steps (a) and (b) recited by the instant claims using the same starting material of human fetal liver, the low density mononuclear cell population of step (c) or the cell samples in which red blood cells were depleted in the method of Craig et al. would inherently contain an enriched population of human liver progenitors having the recited characteristics.

Thus, the reference anticipates the instant claims.

Claims 1, 3-6, 8 and 45-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Reid et al. (U.S. Patent 5,789,246; Cited previously). **This is a new ground of rejection.**

Reid et al. teach a method for the isolation of hepatocyte precursors, said method comprises the steps of: (a) preparing single dissociated liver cells obtained from liver tissue from a mammal including human, (b) subjecting the cells to various procedures including centrigugal elutriation for cells which are smaller than mature hepatocytes to eliminate mature liver cells from the cell population (col. 1, lines 33-64). Reid et al. further teach that the immature cells comprising hepatocyte precursors may alternatively be enriched by contacting cells from an excised section of liver tissue with monoclonal antibodies which recognize an epitope of the hepatocyte precursor cells, so

that the precursor cells can be separated from the remainder cells of the excised tissue (line 65 of col. 1 continues to line 5 of col. 2).

As the method taught by Reid et al. contains the same steps (a) and (b) recited by the instant claims using the same starting material of human liver, the cell population obtained in the method of Reid et al. would inherently contain an enriched population of human liver progenitors having the recited characteristics.

Accordingly, the reference anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 12, 14-19 and 47-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reid et al. (U.S. 5,789,246) in view of Reid et al. (U.S. 6,069,005). **This is a new ground of rejection.**

Reid et al. (U.S. 5,789,246) teach a method for the isolation of hepatocyte precursors, said method comprises the steps of: (a) preparing single dissociated liver cells obtained from liver tissue from a mammal including human, (b) subjecting the cells to various procedures including centrigugal elutriation for cells which are smaller than mature hepatocytes to eliminate mature liver cells from the cell population (col. 1, lines 33-64). Reid et al. further teach that the immature cells comprising hepatocyte precursors may alternatively be enriched by contacting cells from an excised section of liver tissue with monoclonal antibodies which recognize an epitope of the hepatocyte precursor cells, so that the precursor cells can be separated from the remainder cells of the excised tissue (line 65 of col. 1 continues to line 5 of col. 2).

Reid et al. (U.S. 5,789,246) do not specifically teach a method of preparing a composition comprising a mixture of cells comprised of an enriched population of human liver progenitors or human hepatic progenitors of claim 1 or claim 12, wherein the method of claim 1 further comprises selecting those cells which their progeny, or more mature forms thereof exhibiting one or more markers indicative of expression of alpha-fetoprotein, albumin or both or wherein the method further comprises the step of subjecting the debulked suspension to a positive or negative immunoselection.

However, at the effective filing date of the present application (1/19/1999) Reid et al. (U.S. 6,069,005) already disclosed a method of isolating hepatic progenitors from rat

fetal livers utilizing panning techniques and flow cytometry on single cell suspension of liver cells (See claim 1, column 20). The method **comprises** the panning and fluorescence activated cell sorting of fetal liver cells using specific antibodies to remove mature hepatocytes, mature bile duct cells, endothelial cells, mesenchymal cells and hematopoietic cells for obtaining a cell population enriched for immature hepatic cell types which were subsequently separated into distinct subcategories by multiparametric fluorescence activated cell sorting (See Examples I and II). The panning stage involves multiple steps (see Table 3 in col. 6, for example) resulting in isolated cells enriched up to 5-fold for AFP mRNA and 2-fold for albumin mRNA (col. 17, lines 19-27). One of the panning steps is a selecting step for cells exhibiting one or more markers indicative of expression of alpha-protein, albumin or both, for this instance mRNAs of AFP and albumin. It is further noted that fetal liver cells selected for flow cytometry in the disclosed method have a broad range in cell size, 5 to 15 microns (See column 17, lines 50-51). Reid et al. (U.S. 6,069,005) further teach that currently available methods for isolation of hepatoblasts require the use of fractionation methods for cell size or cell density which are inadequate for separating the hemopoietic from the hepatopoietic precursors (col. 4, lines 12-15), while the method utilizing panning techniques and flow cytometry on cell suspensions of liver cells allow rapid reduction of the number of non-hepatoblast cells and the isolation of highly purified distinct subcategories of immature hepatic cell types with good viabilities (see Summary of the Invention; col. 6, lines 38-57).

Accordingly, at the effective filing date of the present application it would have been obvious for an ordinary skilled artisan to modify the method of preparing a composition comprising hepatocyte precursors of Reid et al. (U.S. 5,789,246) by further incorporating the panning and fluorescence activated cell sorting steps taught by Reid et al. (U.S. 6,069,005) to obtain highly purified distinct subcategories of immature hepatic cell types with good viabilities.

An ordinary skilled artisan would have been motivated to carry out the above modification because as clearly taught by Reid et al. (U.S. 6,069,005) that previously available methods for isolating hepatoblasts utilizing the fractionation step for cell size or cell density (including the method of Reid et al. in U.S. 5,789,246) **are inadequate** for separating the hemapoietic from the hepatopoietic precursors (col. 4, lines 12-15), while the method utilizing panning techniques and flow cytometry on cell suspensions of liver cells allow rapid reduction of the number of non-hepatoblast cells and the isolation of highly purified distinct subcategroies of immature hepatic cell types with good viabilities (see Summary of the Invention; col. 6, lines 38-57). It is further noted that the main purpose of the step of subjecting the cells to centrifugal elutriation in the method taught by Reid et al. (U.S. Patent 5,789,246) is for the elimination of mature liver cells from the immature cell population, and not for the separation of hematopoietic from hepatopoietic precursor cells, and there is no explicit teachings in Reid et al. (U.S. Patent 6,069,005) indicating or suggesting that the centrifugal elutriation step should not be used for elimination of mature liver cells from the immature cell population. The modified method

resulting from the combined teachings of Reid et al. (U.S. 5,789,246) in view of Reid et al. (U.S. 6,069,005) is indistinguishable from the instantly claimed invention.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Reid et al. (U.S. 5,789,246) and Reid et al. (U.S. 6,069,005), coupled with a high level of skill of an ordinary skilled artisan in the art.

Accordingly, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636; Central Fax No. (703) 872-9306.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER